ABSTRACT OF THE DISCLOSURE

The present invention relates to methods and compositions for inhibiting cell survival and/or promoting cell death following exposure to cytotoxic agents and stress such as radiation or chemotherapy exposure through inhibition of V-H^+-ATPase. In particular, the formation and/or acidification of acidic vesicular organelles (AVOs) may be prevented or decreased by inhibiting the activity of vacuolar proton ATPase ("V-H^+-ATPase"). The methods and compositions of the invention are based on the observation that (i) following irradiation surviving cancer cells accumulate AVOs and that their acidification is mediated by V-H^+-ATPase; (ii) surviving colonies of cells contain higher levels of AVOs; and (iii) inhibition of V-H^+-ATPase decreases the clonogenic survival of cells irradiated or exposed to chemotherapeutic agents. These observations led to the conclusion that V-H^+-ATPase activity and AVO function serve to protect cells from radiation and chemotherapy damage. In addition, agents such as bFGF, TNF-α, PMA, rapamycin and tamoxifen were shown to be inducers of acidic organelle formation. Therefore signal transduction pathways mediated by these agents provide targets for drug screening assays designed to identify inhibitors of V-H^+-ATPase activity and AVO formation/acidification. The present invention may be used to treat cancer subjects through sensitization of neoplastic cells to the toxic effects of radiation and chemotherapy.